UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/055,711	01/22/2002	Edward Rebar	8325-0025	6236

20855 7590 11/26/2008

ROBINS & PASTERNAK
1731 EMBARCADERO ROAD
SUITE 230
PALO ALTO, CA 94303

EXAMINER	
DUNSTON, JENNIFER ANN	

ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
11/26/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/055,711	REBAR ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 14 October 2008.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,23-28,30-48 and 52-57 is/are pending in the application.

4a) Of the above claim(s) 1,23,24,33-35,38,42-48 and 52 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 25-28,30-32,36,37,39-41 and 53-57 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 22 January 2002 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/30/2008 has been entered.

Receipt is acknowledged of an amendment, filed 9/30/2008, in which claims 2-5 were canceled, and claims 30 and 56 were amended. Claims 1, 23-28, 30-48 and 52-57 are pending.

Election/Restrictions

Applicant elected Group II (drawn to nucleic acid), species: DNA target sequence, zinc finger component comprising X(3)-Cys-X(2)-Cys-X(12)-His-X(3)-Z-X(4), target located in a plant cell, and a maize C1 activation domain in the replies filed on 8/3/2004 and 11/18/2004. This restriction requirement was made FINAL in the Office action mailed 2/9/2005 and reiterated in the Office action mailed 11/15/2005.

The requirement for the election of a specific zinc finger component, as set forth on pages 3-4 of the Office action mailed 7/1/2004 was <u>withdrawn</u> in the Office action mailed 6/14/2206. The remainder of the species election requirement was maintained in the Office action mailed 6/14/2006. Thus, the species election requirements for target sequence type (DNA), where the target is located (plant cell), and functional domain type (C1 activation domain) are maintained.

Claims 1, 33, 42-48 and 52 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the replies filed on 8/3/2004 and 11/18/2004.

Claims 23-24, 34-35 and 38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the replies filed on 8/3/2004 and 11/18/2004.

Currently, claims 25-28, 30-32, 36-37, 39-41 and 53-57 are under consideration.

Claim Objections

Claim 30 is objected to because of the following informalities: the claim recites “the recognition region of zinc-finger binding domain protein"; however this element is not previously recited in the claim. It would be remedial to amend the claim to recite “a recognition helix of the zinc finger binding domain protein.” Claims 25-28, 31-32, 36-37, 39-41 and 53-55 depend from claim 30 and thus are objected to for the same reason. Appropriate correction is required.

Claim 56 is objected to because of the following informalities: the claim requires "a beta turn comprising two amino-terminal zinc coordinating cysteine or histidine residues" at lines 4-5 and later states, "wherein the two amino-terminal zinc coordinating residues are cysteine residues. Because the claim does not encompass embodiments where an amino-terminal zinc coordinating residue is a histidine, it would be remedial to remove the reference to histidine at

lines 4-5. Claim 57 depends from claim 56 and is objected to for the same reasons applied to claim 56. Appropriate correction is required.

Response to Arguments - 35 USC § 112

The rejection of claims 2, 4, 25-28, 30-32, 36, 37, 39-41 and 53-57 under 35 U.S.C. 112, first paragraph, has been withdrawn in view of Applicant's amendment to the claims in the reply filed 9/10/2008. The claims have been amended to require a nucleic acid target sequence. Furthermore, the claims have been amended to exclude the large genus of non-canonical zinc finger structures where all of the zinc coordinating residues are cysteine. The evidence on the record indicates that ordinary artisans could not predict the operability of Cys_4-type zinc fingers other than those species disclosed by the prior art (Green et al. Biochem. J., Vol. 333, pages 85-90, 1998, of record). The claims are now drawn to non-canonical zinc fingers that contain at least one histidine, as a zinc coordinating residue. The prior art indicates that conversion of a canonical CCHH zinc finger to a HHHH zinc finger maintains the beta sheet and alpha helical structure of the zinc finger without abolishing nucleic acid binding activity (Hori et al. J. Am. Chem. Soc. Vol. 122, pages 7648-7653, 2000, and Hori et al. Nucleic Acids Symposium Series No. 44, pages 295-296, 2000; both cited on the IDS filed 2/5/2004). Further, the prior art teaches zinc finger domains comprising a CCHC zinc finger, where the domains are expected to comprise a beta sheet and alpha helix and are capable of binding to a target nucleic acid sequence (Jiang et al. The Journal of Biological Chemistry, Vol. 271, No. 18, pages 10723-10730, 1996, cited on the IDS filed 4/15/2003). The post filing art supports the predictable nature of mutating a canonical CCHH zinc finger to CHHH or HCHH while retaining the

necessary secondary structure to bind a nucleic acid target sequence (Negi et al. Biochemical and Biophysical Research Communications, Vol. 325, pages 421-425, 2004). Given the absence of any contradictory evidence of record, either in the prior art or post filing art, Applicant's disclosure would have allowed the skilled artisan to envisage all recited cysteine/histidine combinations now claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 25-28, 30-32, 36-37, 39-41 and 53-56 are rejected under 35 U.S.C. 102(e) as being anticipated by Barbas, III et al (US Patent No. 7,151,201 B2, cited in a prior action; see the entire reference). The effective date of the reference is 1/19/2001 based upon the lack of disclosure of the C3H zinc finger in the provisional applications. This is a new rejection.

Regarding claims 25-27, 30, 55 and 56, Barbas, III et al teach nucleic acid molecules encoding zinc finger proteins that bind to a target nucleotide sequence of 3, 6, 9, 12, 15 or 18 nucleotides, where the zinc finger protein binds the target nucleotide sequence of the formula $(GNN)_n$, where N is any one of A, T, C or G and n is an integer from 1 to 6 (e.g., column 3, lines 13-43; column 18, lines 48-64; column 19, lines 53-57; Table 2). Barbas, III et al teach the mutagenesis of known zinc finger framework proteins, where three positions on the alpha-helix,

-1, 3 and 6, are involved in specific base contacts (e.g., column 21, lines 8-39). Further, Barbas, III et al teach the use of plant C3H (CCCH) zinc finger proteins as a framework or backbone for the encoded polypeptide (e.g., column 22, lines 51-64). Barbas, III et al teach that the target nucleotide sequence can be present in a plant cell and can be a promoter sequence (e.g., column 3, lines 23-50). Specific plant promoter sequences disclosed by Barbas, III et al include GCG target DNA sequences (e.g., Examples 2 and 3). Further, Barbas III et al teach that the target nucleotide sequence can be endogenous or exogenous to the target gene (e.g., column 3, lines 23-50).

Regarding claim 28, the claims do not impose a strict linear order on the first, second and third zinc fingers. Thus, Barbas, III et al teach the nucleic acid molecule encoding the zinc finger polypeptide where the non-canonical zinc finger is the third zinc finger component, because any one of the at least three zinc fingers can be considered the "third" zinc finger component.

Regarding claims 31-32, Barbas, III et al teach expression vectors comprising the polynucleotide sequences encoding the zinc finger proteins, and plant host cells comprising the vectors (e.g., column 32, lines 10-36).

Regarding claims 36-37 and 39-41, Barbas, III et al teach that the encoded zinc finger protein also includes an activation domain of a regulatory protein, such as a C1 activator domain of maize, in order to activate expression of the target gene operably linked to the target nucleotide sequence (e.g., column 4, lines 42-48; column 25, lines 10-46). Barbas, III et al teach expression vectors comprising the polynucleotide sequences encoding the zinc finger proteins, and plant host cells comprising the vectors (e.g., column 32, lines 10-36).

Regarding claim 53, Barbas, III et al teach the suspension of the polynucleotides in a pharmaceutically acceptable excipient that is an electroporation buffer of 0.3 M mannitol, 5 mM MES, 70 mM KCl, pH 5.8 (e.g., column 55, lines 35-67).

Regarding claim 54, the claims do not impose a strict linear order on the first, second and third zinc fingers. Thus, Barbas, III et al teach the nucleic acid molecule encoding the zinc finger polypeptide where the non-canonical zinc finger is the first zinc finger component, because any one of the at least three zinc fingers can be considered the "first" zinc finger component.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 25-28, 30-32, 36-37, 39-41 and 53-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 7,151,201 B2, cited in a prior action; see the entire reference) in view of Jiang et al (The Journal of Biological Chemistry, Vol. 271, No. 18, pages 10723-10730, 1996, cited on the IDS filed 4/15/2003; see the entire reference). This is a new rejection. This rejection has been included, because the provisional applications do not provide support for the C3H zinc finger discussed in the above rejection made under 35 U.S.C. 102(e).

Barbas, III et al teach nucleic acid molecules encoding zinc finger proteins that bind to a target nucleotide sequence of 3, 6, 9, 12, 15 or 18 nucleotides, where the zinc finger protein binds the target nucleotide sequence of the formula $(GNN)_n$, where N is any one of A, T, C or G and n is an integer from 1 to 6 (e.g., column 3, lines 13-43; column 18, lines 48-64; column 19, lines 53-57; Table 2). Barbas, III et al teach that the target nucleotide sequence can be present in a plant cell and can be a promoter sequence (e.g., column 3, lines 23-50). Specific plant promoter sequences disclosed by Barbas, III et al include GCG target DNA sequences (e.g., Examples 2 and 3). Further, Barbas III et al teach that the target nucleotide sequence can be endogenous or exogenous to the target gene (e.g., column 3, lines 23-50). Barbas, III et al teach that the encoded zinc finger protein also includes an activation domain of a regulatory protein, such as a C1 activator domain of maize, in order to activate expression of the target gene operably linked to the target nucleotide sequence (e.g., column 4, lines 42-48; column 25, lines 10-46). Barbas, III et al teach that two different zinc finger DNA binding domains can be linked together to form one transcription factor and that any zinc fingers may be used (e.g., paragraph bridging columns 11-12; column 18, lines 48-64). Barbas, III et al teach expression vectors

comprising the polynucleotide sequences encoding the zinc finger proteins, and plant host cells comprising the vectors (e.g., column 32, lines 10-36). Barbas, III et al teach the suspension of the polynucleotides in a pharmaceutically acceptable excipient that is an electroporation buffer of 0.3 M mannitol, 5 mM MES, 70 mM KCl, pH 5.8 (e.g., column 55, lines 35-67).

Barbas, III et al do not teach the isolated polynucleotide, where the polynucleotide encodes a non-canonical zinc finger component comprising a beta turn comprising two amino-terminal zinc coordinating cysteine residues and an alpha helix comprising one carboxy-terminal zinc coordinating histidine residue and one carboxy-terminal cysteine residue, where the carboxy-terminal histidine residue is amino terminal to the carboxy-terminal cysteine residue.

Jiang et al teach a nucleic acid molecule encoding a Cys-Cys, His-Cys zinc finger protein (e.g., paragraph bridging pages 10723-10724; Figure 1). The protein, referred to as neural zinc finger factor 1 (NZF-1), contains two separate Cys-Cys, His-Cys type zinc finger DNA binding domain, each of which can bind independently to similar DNA sequences (e.g., paragraph bridging pages 10723-10724; Figure 1). Jiang et al teach that the zinc finger domains are expected to fold into a beta sheet and an alpha helix (e.g., page 10727, paragraph bridging columns). Jiang et al teach that optimal binding of the two Cys-Cys, His-Cys type zinc fingers occurs with the AAGTT target nucleic acid sequence (e.g., paragraph bridging pages 10727-10728).

Because Barbas, III et al disclose nucleic acid molecules encoding any zinc finger protein, and Jiang et al teach a nucleic acid molecule encoding a zinc finger protein, it would have been obvious to one or ordinary skill in the art at the time the invention was made to include the sequence encoding the Cys-Cys, His-Cys zinc fingers capable of binding AAGTT of

Jiang et al in the nucleic acid molecules of Barbas, III et al, such as those encoding zinc fingers containing a recognition helix that is engineered to bind the GCG target nucleic acid sequence, to achieve the predictable result of making a polynucleotide that encodes a zinc finger polypeptide that binds to a plant promoter sequence containing the target nucleic acid sequence of the combined zinc fingers of Barbas, III et al and Jiang et al. With respect to claims 28 and 54, which require the non-canonical zinc finger component to be the third zinc finger component or the first zinc finger component, respectively, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the zinc finger so Barbas III et al and Jiang et al in an order from N-terminus to C-terminus such that the non-canonical zinc fingers are present at the first and/or third zinc fingers. However, it is noted that the claims do not explicitly impose a linear order to the first, second and third zinc fingers.

Furthermore, one would have been motivated to include the sequence encoding the Cys-Cys, His-Cys type zinc fingers of Jiang et al in order to expand the repertoire of available zinc finger nucleotide-binding proteins encoded by the polynucleotides. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 25-28, 30-32, 36, 39-41 and 53-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 6,242,568, cited as reference A39 on the IDS filed 5/11/2005; see the entire reference) in view of Jiang et al (The Journal of Biological

Chemistry, Vol. 271, No. 18, pages 10723-10730, 1996, cited on the IDS filed 4/15/2003; see the entire reference). This is a new rejection.

Barbas, III et al teach polynucleotides encoding zinc finger-nucleotide binding polypeptides in combination with a pharmaceutically acceptable carrier (e.g., column 2, line 66 to column 3, line 17; column 4, lines 48-65; column 7, line 56 to column 8, line 54). Barbas, III et al teach recombinant expression vectors comprising the polynucleotides, and host cells such as plant cells comprising the vectors (e.g., column 18, line 47 to column 20, line 56; column 26, lines 38-46). Barbas, III et al teach that the zinc finger binding motif (i.e., target nucleic acid sequence) can be any sequence designed by the experiment or to which the zinc finger protein binds, and the motif may be found in any DNA or RNA sequence, including regulatory sequences such as a promoter sequence (e.g., column 5, line 11 to column 6, line 62). The target nucleotide sequence may be a sequence in a plant cell, whether it is a plant nucleotide sequence or a sequence that is not naturally occurring in the cell (e.g., column 5, lines 52-65; column 7, lines 40-48; column 26, lines 38-46). Barbas, III et al teach that the encoded zinc finger protein can be a variant, mutagenized protein and/or an expanded zinc finger protein having as many as 12 zinc fingers, which will bind a sequence of up to 36 contiguous base pairs (e.g., paragraph bridging columns 4-5; column 7, lines 20-55). Barbas, III et al teach that zif268 is a zinc finger protein that can be mutagenized and/or expanded (e.g., column 7, lines 40-55). Barbas et al specifically teach variants of zif268 zinc fingers that bind to the triplets GCG, TGT, TGG, TTG, and CTG (e.g., Figure 9). Further, Barbas, III et al teach embodiments where the polynucleotides encode the zinc finger-nucleotide binding polypeptides that are transcriptional activators in plants, and thus contain an activation domain (e.g., column 26, lines 38-58).

Barbas, III et al do not teach the isolated polynucleotide, where the polynucleotide encodes a non-canonical zinc finger component comprising a beta turn comprising two amino-terminal zinc coordinating cysteine residues and an alpha helix comprising one carboxy-terminal zinc coordinating histidine residue and one carboxy-terminal cysteine residue, where the carboxy-terminal histidine residue is amino terminal to the carboxy-terminal cysteine residue.

Jiang et al teach a nucleic acid molecule encoding a Cys-Cys, His-Cys zinc finger protein (e.g., paragraph bridging pages 10723-10724; Figure 1). The protein, referred to as neural zinc finger factor 1 (NZF-1), contains two separate Cys-Cys, His-Cys type zinc finger DNA binding domain, each of which can bind independently to similar DNA sequences (e.g., paragraph bridging pages 10723-10724; Figure 1). Jiang et al teach that the zinc finger domains are expected to fold into a beta sheet and an alpha helix (e.g., page 10727, paragraph bridging columns). Jiang et al teach that optimal binding of the two Cys-Cys, His-Cys type zinc fingers occurs with the AAGTT target nucleic acid sequence (e.g., paragraph bridging pages 10727-10728).

Because Barbas, III et al disclose nucleic acid molecules encoding assembled zinc finger domains, and Jiang et al teach a nucleic acid molecule encoding zinc finger domains, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include the sequence encoding the Cys-Cys, His-Cys zinc fingers capable of binding AAGTT of Jiang et al in the nucleic acid molecules of Barbas, III et al, such as those encoding zinc fingers containing a recognition helix that is engineered to bind the GCG, TGT, TGG, TTG or CTG target nucleic acid sequence, to achieve the predictable result of making a polynucleotide that encodes a zinc finger polypeptide that binds to a plant promoter sequence containing the target

nucleic acid sequence of the combined zinc fingers of Barbas, III et al and Jiang et al. With respect to claims 28 and 54, which require the non-canonical zinc finger component to be the third zinc finger component or the first zinc finger component, respectively, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the zinc finger of Barbas, III et al and Jiang et al in an order from N-terminus to C-terminus such that the non-canonical zinc fingers are present at the first and/or third zinc fingers. However, it is noted that the claims do not explicitly impose a linear order to the first, second and third zinc fingers.

Furthermore, one would have been motivated to include the sequence encoding the Cys-Cys, His-Cys type zinc fingers of Jiang et al in order to expand the repertoire of available zinc finger nucleotide-binding proteins encoded by the polynucleotides. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 6,242,568, cited as reference A39 on the IDS filed 5/11/2005; see the entire reference) in view of Jiang et al (The Journal of Biological Chemistry, Vol. 271, No. 18, pages 10723-10730, 1996, cited on the IDS filed 4/15/2003; see the entire reference) as applied to claims 2, 4, 25-28, 30-32, 36, 39-41 and 53-55 above, and further in view of Guyer et al (Genetics, Vol. 149, pages 633-639, 1998, cited in a prior action; see the entire reference). This is a new rejection.

The combined teachings of Barbas, III et al and Jiang et al are described above and applied as before.

Barbas, III et al and Jiang et al do not teach the polynucleotide where the activation domain is a maize C1 activation domain.

Guyer et al teach *Arabidopsis* plants comprising a stably integrated hybrid transcription factor, and plants comprising an activatable transgene, where the hybrid transcription factor and activatable transgene are brought together in the same cell by fertilization (e.g. paragraph bridging pages 633-634). Specifically, Guyer et al teach a GAL4 DNA binding domain fused to a maize C1 transcription activation domain as the hybrid transcription factor, and a reporter transgene controlled by a synthetic promoter comprising ten GAL4 DNA binding sites (e.g. paragraph bridging pages 633-634; Figure 1). Further, Guyer et al teach that many positive transcriptional regulatory factors are modular, consisting of a DNA-binding domain and an activation domain and that fusing combinations of these elements derived from different kingdoms results in the production of diverse hybrid factors having defined DNA-binding specificity and transcriptional activation function with advantages over expression under direct control by a natural promoter (e.g. page 633, left column; page 638, paragraph bridging columns).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the polynucleotide to comprise a C1 activation domain taught by Guyer et al because Barbas, III et al teach it is within the skill of the art to make a plant cell comprising the polynucleotide where the polynucleotide encodes a zinc finger-nucleotide binding polypeptide that activates expression of a gene operably linked to the target nucleotide sequence, and Guyer

et al teach that the maize C1 activation domain functions in a plant cell to activate transcription from a heterologous DNA binding domain.

One would have been motivated to specifically use the maize C1 activation domain, because it was known in the art to function in plants. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 25-28, 30-32, 36, 39-41 and 53-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 6,242,568, cited as reference A39 on the IDS filed 5/11/2005; see the entire reference) in view of Hori et al (J. Am. Chem. Soc. Vol. 122, pages 7648-7653, July 29, 2000, cited on the IDS filed 2/5/2004; see the entire reference). This is a new rejection.

Barbas, III et al teach polynucleotides encoding zinc finger-nucleotide binding polypeptides in combination with a pharmaceutically acceptable carrier (e.g., column 2, line 66 to column 3, line 17; column 4, lines 48-65; column 7, line 56 to column 8, line 54). Barbas, III et al teach recombinant expression vectors comprising the polynucleotides, and host cells such as plant cells comprising the vectors (e.g., column 18, line 47 to column 20, line 56; column 26, lines 38-46). Barbas, III et al teach that the zinc finger binding motif (i.e., target nucleic acid sequence) can be any sequence designed by the experiment or to which the zinc finger protein binds, and the motif may be found in any DNA or RNA sequence, including regulatory sequences such as a promoter sequence (e.g., column 5, line 11 to column 6, line 62). The target

nucleotide sequence may be a sequence in a plant cell, whether it is a plant nucleotide sequence or a sequence that is not naturally occurring in the cell (e.g., column 5, lines 52-65; column 7, lines 40-48; column 26, lines 38-46). Barbas, III et al teach that the encoded zinc finger protein can be a variant, mutagenized protein and/or an expanded zinc finger protein having as many as 12 zinc fingers, which will bind a sequence of up to 36 contiguous base pairs (e.g., paragraph bridging columns 4-5; column 7, lines 20-55). Barbas, III et al teach that zif268 is a zinc finger protein that can be mutagenized and/or expanded (e.g., column 7, lines 40-55). Barbas et al specifically teach variants of zif268 zinc fingers that bind to the triplets GCG, TGT, TGG, TTG, and CTG (e.g., Figure 9). Further, Barbas, III et al teach embodiments where the polynucleotides encode the zinc finger-nucleotide binding polypeptides that are transcriptional activators in plants, and thus contain an activation domain (e.g., column 26, lines 38-58).

Barbas, III et al do not teach the isolated polynucleotide, where the polynucleotide encodes a non-canonical zinc finger component comprising a beta turn comprising two amino-terminal zinc coordinating histidine residues and an alpha helix comprising two carboxy-terminal zinc coordinating histidine residues.

Hori et al teach a DNA molecule encoding three zinc fingers of the Sp1 transcription factor where the three zinc fingers are each mutated to replace the two zinc coordinating cysteine residues with histidine residues, resulting in three non-canonical zinc fingers each comprising a beta turn comprising two amino-terminal zinc coordinating histidine residues and an alpha helix comprising two carboxy-terminal zinc coordinating histidine residues (e.g., page 7649, Preparations of Zinc Finger Proteins C_2H_2Sp1 and H_4Sp1; page 7653, right column; Figure 1). The protein is referred to as H_4Sp1. Hori et al teach that the H_4Sp1 protein is capable of binding

the Sp1 nucleic acid recognition site, the GC box sequence 5'-GGGGCGGGGCC-3' (e.g., paragraph bridging pages 7651-7652).

Because Barbas, III et al disclose nucleic acid molecules encoding assembled zinc finger domains, and Hori et al teach a DNA molecules encoding zinc finger domains, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include the sequence encoding the His_4 zinc fingers capable of binding the GC box sequence of Hori et al in the nucleic acid molecules of Barbas, III et al, such as those encoding zinc fingers containing a recognition helix that is engineered to bind the GCG, TGT, TGG, TTG or CTG target nucleic acid sequence, to achieve the predictable result of making a polynucleotide that encodes a zinc finger polypeptide that binds to a plant promoter sequence containing the target nucleic acid sequence of the combined zinc fingers of Barbas, III et al and Hori et al. With respect to claims 28 and 54, which require the non-canonical zinc finger component to be the third zinc finger component or the first zinc finger component, respectively, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the zinc finger of Barbas, III et al and Hori et al in an order from N-terminus to C-terminus such that the non-canonical zinc fingers are present at the first and/or third zinc fingers. However, it is noted that the claims do not explicitly impose a linear order to the first, second and third zinc fingers.

Furthermore, one would have been motivated to include the sequence encoding the His_4 zinc fingers of Hori et al in order to expand the repertoire of available zinc finger nucleotide-binding proteins encoded by the polynucleotides. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the

contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 6,242,568, cited as reference A39 on the IDS filed 5/11/2005; see the entire reference) in view of Hori et al (J. Am. Chem. Soc. Vol. 122, pages 7648-7653, July 29, 2000, cited on the IDS filed 2/5/2004; see the entire reference) as applied to claims 25-28, 30-32, 36, 39-41 and 53-55 above, and further in view of Guyer et al (Genetics, Vol. 149, pages 633-639, 1998, cited in a prior action; see the entire reference). This is a new rejection.

The combined teachings of Barbas, III et al and Hori et al are described above and applied as before.

Barbas, III et al and Hori et al do not teach the polynucleotide where the activation domain is a maize C1 activation domain.

Guyer et al teach *Arabidopsis* plants comprising a stably integrated hybrid transcription factor, and plants comprising an activatable transgene, where the hybrid transcription factor and activatable transgene are brought together in the same cell by fertilization (e.g. paragraph bridging pages 633-634). Specifically, Guyer et al teach a GAL4 DNA binding domain fused to a maize C1 transcription activation domain as the hybrid transcription factor, and a reporter transgene controlled by a synthetic promoter comprising ten GAL4 DNA binding sites (e.g. paragraph bridging pages 633-634; Figure 1). Further, Guyer et al teach that many positive transcriptional regulatory factors are modular, consisting of a DNA-binding domain and an activation domain and that fusing combinations of these elements derived from different

kingdoms results in the production of diverse hybrid factors having defined DNA-binding specificity and transcriptional activation function with advantages over expression under direct control by a natural promoter (e.g. page 633, left column; page 638, paragraph bridging columns).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the polynucleotide to comprise a C1 activation domain taught by Guyer et al because Barbas, III et al teach it is within the skill of the art to make a plant cell comprising the polynucleotide where the polynucleotide encodes a zinc finger-nucleotide binding polypeptide that activates expression of a gene operably linked to the target nucleotide sequence, and Guyer et al teach that the maize C1 activation domain functions in a plant cell to activate transcription from a heterologous DNA binding domain.

One would have been motivated to specifically use the maize C1 activation domain, because it was known in the art to function in plants. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 6,242,568, cited as reference A39 on the IDS filed 5/11/2005; see the entire reference) in view of Hori et al (J. Am. Chem. Soc. Vol. 122, pages 7648-7653, July 29, 2000, cited on the IDS filed 2/5/2004; see the entire reference) as applied to claims 25-28, 30-32, 36, 39-41 and 53-55 above, and further in view of Jiang et al (The Journal of Biological

Chemistry, Vol. 271, No. 18, pages 10723-10730, 1996, cited on the IDS filed 4/15/2003; see the entire reference). This is a new rejection.

The combined teachings of Barbas, III et al and Hori et al are described above and applied as before. Further, Hori et al teach that zinc finger proteins acquire DNA binding ability by Zn(II) complexation, and the utilization of metal-ligation is advantageous for designing a minidomain, such as a metallofinger motif, possessing DNA binding ability (e.g., page 7648, paragraph bridging columns). Hori et al teach that in nature, Cys_2His_2-, Cys_3His-, Cys_4, and Cys_6-type zinc fingers exist (e.g., page 7648, right column, full paragraph). The Cys_2His_2-type zinc fingers are known to possess the following characteristics: (1) compact ββα fold, which is acquired by Zn(II)-coordination to bind the asymmetric DNA sequence, (2) one finger recognizes 3 to 4 base pairs by the side chains of amino acids located on the recognition helix, and (3) extended recognition can be attained by tandem repeating (e.g., page 7648, right column, full paragraph). Hori et al teach that the ββα fold of the Cys_2His_2-type zinc finger is an attractive framework for designing novel framework motifs, where the canonical zinc coordinating residues are replaced (e.g., page 7648, right column, full paragraph).

Barbas, III et al and Hori et al do not teach the polynucleotide encoding a non-canonical zinc finger domain, where the amino-terminal zinc coordinating residues are cysteine, and the carboxy-terminal zinc coordinating residues include a cysteine and histidine, where the carboxy-terminal zinc coordinating histidine residue is amino terminal to the carboxy-terminal zinc coordinating cysteine residue.

Jiang et al teach a nucleic acid molecule encoding a Cys-Cys, His-Cys zinc finger protein (e.g., paragraph bridging pages 10723-10724; Figure 1). The protein, referred to as neural zinc

finger factor 1 (NZF-1), contains two separate Cys-Cys, His-Cys type zinc finger DNA binding domain, each of which can bind independently to similar DNA sequences (e.g., paragraph bridging pages 10723-10724; Figure 1). Jiang et al teach that the zinc finger domains are expected to fold into a beta sheet and an alpha helix (e.g., page 10727, paragraph bridging columns). Jiang et al teach that optimal binding of the two Cys-Cys, His-Cys type zinc fingers occurs with the AAGTT target nucleic acid sequence (e.g., paragraph bridging pages 10727-10728).

Because Hori et al teach that cysteine or histidine residues coordinate zinc ions in metallofinger proteins, and that cysteine and histidine can be interchanged while retaining secondary structure and DNA binding ability, and because Jiang et al teach that $Cys_2HisCys$ structures exist in nature, it would have been obvious to one of ordinary skill in the art at the time the invention was made to replace the Cys_2His_2 zinc coordinating residues of Sp1 zinc fingers taught by Hori et al with $Cys_2HisCys$ zinc coordinating residues. The art teaches that both cysteine and histidine coordinate zinc ions in the metallofinger structure, and Hori et al teach the desirability of using different combinations of coordinating residues other than Cys_2His_2. Thus, it would have been obvious to a person of ordinary skill in the art to try the $Cys_2HisCys$ combination of zinc coordinating residues within the Sp1 zinc finger structure taught by Hori et al, as a person with ordinary skill has good reason to pursue the known options within his or her technical grasp. The $Cys_2HisCys$ structure would be expected to retain the secondary structure and DNA binding ability taught by Hori et al.

Furthermore, one would have been motivated to include the sequence encoding the $Cys_2HisCys$ zinc finger in order to expand the repertoire of available zinc finger nucleotide-

binding proteins encoded by the polynucleotides. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments - 35 USC § 103

The rejection of claims 2, 4, 25-28, 30-32, 36-37, 39-41 and 53-55 under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 7,151,201 B2) in view of Green et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 9/30/2008. The claims have been amended to exclude the Cys_4 structure taught by Green et al.

The rejection of claims 2, 4, 25-28, 30-32, 36, 39-41 and 53-55 under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 6,242,568) in view of Green et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 9/30/2008. The claims have been amended to exclude the Cys_4 structure taught by Green et al.

The rejection of claim 37 under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 6,242,568) in view of Green et al further in view of Guyer et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 9/30/2008. The claims have been amended to exclude the Cys_4 structure taught by Green et al.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.
Examiner
Art Unit 1636

/JD/

/Celine X Qian /
Primary Examiner, Art Unit 1636